REMARKS

The Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Status of the Claims

Original claims 1-14 are cancelled, and claims 15-25 are added. New claim 15 represents an amended claim 14. No new matter has been added, and claims 15-25 are currently pending to be examined on the merits. Support for the new claims is provided as a table below:

Claim	Support (in the Specification as filed)
15	Page 4, lines 9-13 Page 5, lines 32-33 Page 7, 11-15 Page 8 , lines 2-4 Page 11, lines 4-6
16	Original claim 14
17	Page 5, lines 24-26
18	Page 8, lines 2-4
19	Page 8, lines 2-4
20	Page 5, lines 24-26 Page 8, lines 2-4
21	Original claim 7 Page 19, lines 29-31
22	Original claim 1 Page 19, lines 9-10
23	Original claim 10 Page 20, lines 7-12
24	Page 4, lines 9-13 Page 5, lines 32-33 Page 7, 11-15 Page 8 , lines 2-4 Page 11, lines 4-6 Page 19, lines 9-10 Page 19, lines 29-31 Pages 20, lines 7-12
25	Page 1, lines 4-7

II. 35 U.S.C. § 112 Rejections

Original claims 1, 4, 7, 10, and 13 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Applicants respectfully submit that the new claims have overcome the formality rejections, and thus respectfully request withdrawal of the rejections.

II. 35 U.S.C. § 102 Rejections

Original claims 1-3, 7-12 are rejected under 35 U.S.C. § 102(b) as being anticipated by Lilliott (WO 01/35941). The Applicants respectfully disagree and traverse the rejections.

Without acquiescing to the grounds of rejections, the Applicants have amended the claims. Nowhere does Lilliott disclose a preparation wherein the ratio of the median size of the particles of biguanide to the median size of the particles of pioglitazone or a salt thereof is 0.5 to 15, and wherein the particles of pioglitazone or a salt thereof have a median size of 1-25 μm and the particles of biguanide have a median size of 10-100 μm, as recited in independent claims 15 and 24. The Office has also acknowledged that Lilliott does not teach the ratio of median size between the biguanide and pioglitazone. *See* page 6, Office Action.

Because Lilliott does not teach every element recited in the present claims, the former cannot anticipate the latter. Thus, the Applicants respectfully request that the anticipation rejections be withdrawn.

III. 35 U.S.C. § 103 Rejections

Original claims 4-6 are rejected under 35 U.S.C. § 103(a) as being obvious over Lilliott, further in view of Zhuang (*Practical Pharm. Prep. Tech.*, January 1999, p203-04), claims 13-14 as being obvious over Cutie (WO 01/82875), further in view of Zhuang. The Applicants respectfully disagree and traverse the rejections.

A. Current Obviousness Standard

The Supreme Court recently reaffirmed the Graham factors for determining obviousness in *KSR Int'l Co. v. Teleflex Inc.* (No. 04-1350) (U.S., April 30, 2007). The Graham factors, as outlined by the Supreme Court in *Graham et al. v. John Deere Co. of Kansas City et al.*, 383 U.S. 1 (1966), are: 1) determining the scope and contents of the prior art; 2) ascertaining the differences between the claimed invention and the prior art; 3) resolving the level of ordinary skill in the pertinent art; and 4) evaluating evidence of secondary consideration. The Supreme Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a), and held that the proper inquiry for determining obviousness is whether the improvement is more than the predictable use of prior art elements according to their established functions. The Court noted that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed, and specifically stated:

> Often, it will be necessary . . . to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was ***an apparent reason to combine the known elements in the fashion claimed*** by the patent at issue. To facilitate review, this analysis should be made explicit.

KSR Int'l Co. v. Teleflex Inc., slip op. at 14 (emphasis added). As discussed below, the cited art cannot render the claimed invention obvious.

B. Lilliott, Cutie, and/or Zhuang

(i) Lilliott and/or Zhuang does not render the present application obvious

The solid preparation recited in the pending claims have the following features: (i) a phase wherein a pioglitazone or a salt thereof and a biguanide are uniformly dispersed, and (ii)

the ratio of the median size of the particles of biguanide to the median size of the particles of pioglitazone or a salt thereof is 0.5 to15.

Lilliott also teaches that "all thiazolidinediones would be subject to similar decomposition due to the presence of metformin hydrochloride and/or PVP" (*see*, page 2, lines 6-7, Lilliott). Additionally, regarding the homogeneous admixture, Examples 15-18 of Lilliott teach that thiazolidinedione and metformin hydrochloride are each dispersed within its own pharmaceutically acceptable carrier (*see* Abstract, Lilliott). Nowhere does Lilliott teach or suggest a preparation comprising a phase comprising both pioglitazone and biguanide particles that are uniformly dispersed in the preparation. Additionally, as described previously, Lilliott does not teach or suggest the specific ratio of median sizes between the particles of biguanide and those of pioglitazone or a salt thereof, as recited in independent claims 15 and 24.

Zhuang provides a general production method of a tablet, comprising necessarily pulverizing and sieving before forming a mixture to have a smaller particle size, as well as the same size as possible for the ingredients. *See,* the penultimate paragraph in section 1 ("Uniformly mixing each ingredient in the tablet") in the English translation of Zhuang. Nowhere does Zhuang teach or suggest having a final product comprising two components with a specific median particle size ratio or median particle sizes, as recited in the present claims. A "median size," as defined in the present application, refers to the particle size that divides crude particles from fine granules at 50%, each in weight distribution or number distribution (*see,* page 6, lines 17-24, page 25, lines 13-15). Thus, "pulverizing" and/or "sieving" of Zhuang cannot reach the specific median size ratio and/or the median sizes, as recited in the independent claims 15 and 24, and their dependent claims.

Thus, one of ordinary skill in the art would not have been motivated to combine Lilliott with Zhuang to reach the present claims. *See, KSR Int'l Co.* Therefore, Lilliott, Zhuang, or a combination thereof, does not render the present claims obvious.

(ii) Cutie and/or Zhuang does not render the present application obvious

Cutie discloses a "core formulation" comprising pioglitazone and biguanide in separate phases (*see,* Abstract, Cutie), which is further evidenced in the Specification of Cutie, where it states "the first layer should comprise pioglitazone hydrochloride because its dose requirement is lower compared to metformin." (page 2, lines 26-30). Thus, Cutie does not teach or suggest at all the two features of the preparation recited in the present claims – (i) a preparation having a phase comprising uniformly dispersed particles of two components, and (ii) the components having a specific median particle size and ratio.

Thus, in addition to the distinction regarding Zhuang as described above, one of ordinary skill in the art would not have been motivated to combine Cutie with Zhuang to reach the preparation as recited in the present claims. *See, KSR Int'l Co.* Therefore, Cutie, Zhuang, or a combination thereof, does not render the present claims obvious.

The Applicants respectfully request that all obviousness rejections be withdrawn.

CONCLUSION

The Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information

resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date Nov. 7, 2008

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5569
Facsimile: (202) 672-5399

Stephen B. Maebius
Attorney for Applicants
Registration No. 35,264